Cognitive Training Interventions for Patients with Alzheimer's Disease : A Systematic Review

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Cognitive training interventions for patients with Alzheimer's disease: A systematic review

ABSTRACT

Background: Cognitive training (CT) refers to guided cognitive exercises designed to improve specific cognitive functions, as well as enhance performance in untrained cognitive tasks. Positive effects of CT on cognitive functions in healthy elderly people and persons with mild cognitive impairment have been reported, but data regarding the effects of CT in patients with dementia is unclear. *Objective:* We systematically reviewed the current evidence from randomized controlled trials (RCTs) to find out if CT improves or stabilizes cognition and/or everyday functioning in patients with mild and moderate Alzheimer's disease. *Findings:* Altogether, 31 RCTs with CT as either the primary intervention or part of a broader cognitive or multi-component intervention were found. A positive effect was reported in 24 trials, mainly on global cognition and training-specific tasks, particularly when more intensive or more specific CT programs were used. Little evidence of improved everyday functioning was found. *Conclusions:* Despite some positive findings, the inaccurate definitions of CT, inadequate sample sizes, unclear randomization methods, incomplete datasets at follow-up and multiple testing may have inflated the results in many trials. Future high quality RCTs with appropriate classification and specification of cognitive interventions are necessary to confirm CT as an effective treatment option in Alzheimer's disease.

KEYWORDS

Alzheimer's disease, Cognition, Cognitive training, Dementia, Systematic review

INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative condition, leading to deterioration of memory and other cognitive abilities, as well as functional abilities needed for independent living. As the overall number of persons with AD and other dementias is constantly increasing [1], it is particularly important to develop effective, targeted treatments to delay the cognitive and functional decline associated with these diseases. Interventions can be pharmacological, non-pharmacological, or both. At present, medications such as cholinesterase inhibitors and memantine provide limited benefits, and interest in non-pharmacological treatments for cognitive decline is growing [2-6].

The diversity of cognition-related interventions for persons with dementia has expanded during the evolution of non-pharmacological treatments. The interventions are typically classified into three broad categories: cognitive stimulation, cognitive training and cognitive rehabilitation, which are based on different theoretical constructs of restoration and compensation [7, 8]. Cognitive stimulation (CS) is usually administered in a group setting, is often recreational in nature and involves non-specific cognitive activities [4, 7]. Group discussions, reality orientation and reminiscence therapy are examples of cognitive stimulation techniques. Cognitive training (CT) is defined as guided practice on a set of standard tasks designed to reflect particular cognitive functions such as memory, attention or executive functions [5, 7]. Training is assumed to improve, or at least stabilize, performance in a given cognitive domain (i.e. near transfer effect). CT is based on the principles of neuronal plasticity and restoration of cognitive abilities, but also generalized effects beyond the immediate training context are expected (i.e. far transfer effects). Cognitive rehabilitation (CR) refers to more individualized approaches in which personally relevant goals are

identified, and inclusive treatments and compensatory strategies are adopted to manage symptoms, and increase daily functioning [7, 8]. The focus in CR is more on far transfer effects of rehabilitation. These three intervention concepts have been used almost interchangeably in the past, and lack of precision in categorizing cognitive interventions is still present in many trials. Furthermore, many intervention programs combine CT techniques with other methods of rehabilitation, adding to the ambiguity.

Since the earliest randomized controlled trials (RCTs) on CT for patients with dementia, an increasing number of studies have been conducted on the efficacy and feasibility of cognitive-based interventions for AD and other dementias. Trials have evolved from first 'in vivo' clinical trials conducted at treatment facilities to few large-scale well-controlled trials conducted at more than one medical center or clinic. At present, evidence regarding the effects of CS on individuals with dementia is fairly consistent [4, 9], as well as the effects of CT on healthy elderly [10, 11], and mild cognitive impairment (MCI) [6]. Less is known, however, about the effects of CT on dementia. Some earlier reviews have shown emerging evidence for the effectiveness of CT interventions [2, 3], while systematic reviews focusing on CT strictly in RCTs have yielded more tentative results [12-14]. The latest Cochrane review of 12 published RCTs through year 2012 found little, or no evidence for the benefit of CT in AD and vascular dementia [5]. Findings from two meta-analyses of CT on dementia vary from moderate-sized positive effects [15] to no evidence of efficacy [16]. Sitzer et al.'s study focused on earlier small sample trials [15], whereas Huntley et al. reported four CT trials and seven mixed CT/CS trials, but found no evidence of improvement in general cognition outcomes [16].

The public interest in CT, or brain training, for patients with dementia is growing. At the same time, new trials have been published since the latest Cochrane review [5], systematic reviews [13, 14] and meta-analysis [16]. Besides incorporating new trials, we want to introduce stricter distinction between restorative CT, multi-component cognitive interventions and compensatory CT, which have often been mixed up in previous reviews. Furthermore, we report outcomes of the included RCTs across different domains of cognition. Additionally, we include several - but often neglected - factors important to consider when evaluating trials of cognition-based intervention. The duration, frequency and focus of the training, concurrent treatments, baseline cognitive status of the participants and the type of control condition may all have impact on the outcome of the intervention. The follow-up period should also be considered when evaluating the efficacy of a CT treatment. These aspects in mind, we systematically reviewed if CT can improve - or delay the deterioration of - cognition or functional outcome in patients with dementia, predominantly of the Alzheimer's type. Specifically, we wanted to focus on persons in the mild and moderate stages of dementia, as opposed to those in preclinical stages of the disease or at-risk elderly participants.

METHODS

This systematic review adheres to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [17]; however, our protocol was not registered.

Eligibility criteria

The trials selected in this review had to meet the following criteria: were an RCT, included participants with clinically diagnosed or probable AD, used CT as the primary intervention or

included CT as part of a multi-component training or cognitive rehabilitation, included cognition as one of the outcome measures and this outcome had to be assessed using neuropsychological or cognitive tests. CT was defined as repeated practice on cognitively challenging tasks at least once a week for one month, including drill-and-practice exercises and/or strategy training. For studies that used CT in combination with other interventions (e.g. CS or psychomotor activities), we included only those that clearly described CT as a part of their intervention. Studies using only participants with MCI, or elderly people at-risk for dementia were excluded.

Information sources and study selection

MEDLINEÒ, Cochrane Library, DARE and PsycINFO databases were systematically searched for RCTs using terms related to cognitive interventions, Alzheimer's disease and dementia: ('cognitive training' OR 'memory training' OR 'cognitive rehabilitation' OR 'cognitive intervention') AND ('Alzheimer*' OR 'dement*' OR 'memory disorder'). No limits were applied. The initial search was performed in May 2015 and repeated in January and April 2016. The date of the last search was 27 April 2016. Additional RCTs were identified from the reference lists of relevant studies and previous systematic reviews on the topic.

The titles of identified papers were first reviewed for obvious exclusions, and also studies not written in English were excluded. If it was unclear whether the article should be excluded after reading the abstract, the full text was reviewed. Authors ELK and KP compared their reviews of articles to ensure that the same studies had been excluded or included. No metric of inter-rater reliability was assessed.

Methodological quality

Two reviewers (ELK and KP) independently evaluated the included studies according to 10 criteria of methodological quality, and few disagreements were discussed between the reviewers until a consensus was reached. A statistician (HK) participated in the evaluation of the methodological quality of the statistical analyses performed in the trials. We used a modified rating system for evaluation. In this rating system, we applied the criteria for randomized intervention trials used by Cochrane and collaborators [19] as well as the Delphi list [20], which is a criteria list for the quality assessment of randomized clinical trials. We also applied the criteria developed by the Evidence-Based Medicine Working Group [21]. The 10 criteria for our rating system are described in Table 1. Each criterion was considered to be worth 1 point. The methodological quality of the research was considered to be high when a study scored 8-10 points, while scores of 5-7 indicated moderate quality and scores < 5 low quality.

Data collection and coding

Outcome measures included pre- and post-intervention scores on at least one objective test of cognition, typically showing near transfer effects (i.e. within the same cognitive domain as that trained, using non-identical or untrained tasks). When standard cognitive tests were used, each outcome was coded into a cognitive domain based on the categorization provided by Strauss et al. [18]. Memory functions were divided into two categories, namely short-term working memory and long-term episodic memory. Other, non-standard cognitive outcome measures were classified as training-specific outcomes. An outcome was recorded as positive,

when there was a statistically significant difference between intervention and control groups, either because of the improvement of an intervention group, or deterioration of a control group. When available, positive functional outcomes indicating far transfer effects (i.e. mood, behavioral symptoms, activities of daily living; ADL, or quality of life; QoL) were also reported.

We estimated the magnitude of effect sizes (ESs) of general cognitive functioning on the methodologically well-conducted trials (i.e. rated in this review as being of moderate or high quality), when possible. If the magnitude of effect was reported in a trial, we retrieved the figures from the article. The magnitude of effect was interpreted case-by-case as small, medium or large, based on the measure of ES used in each case.

RESULTS

Study selection

We found 31 RCTs that examined the effects of CT on cognition in subjects with AD. Of the 31 RCTs, 19 were found directly from database searches [23-41] and seven additional articles [42-48] were mentioned in reviews [2, 5, 12, 16]. The original May 2015 database search was repeated in January and April 2016, and five more studies were found [49-53]. The results of the selection process are shown in Fig. 1.

Characteristics of included studies

Table 2 presents the characteristics of the 31 RCTs. Several studies combined CT with other cognition-based interventions, such as cognitive stimulation [29, 45, 48, 49, 53] or cognitive rehabilitation techniques [26, 27, 33, 35, 41, 50]. Additionally, physical activities [45, 48] and functional ADL-training [29, 32, 41, 49] were sometimes part of a cognitive intervention program. For further evaluation the studies were divided into three categories: studies with CT as the primary intervention (n=19), studies with CT as part of a multi-component intervention (n=5) and studies with the primary goal of compensating for cognitive impairments (n=7), where the cognitive intervention was closer to cognitive rehabilitation than restorative CT (see Table 2).

The most frequently used CT intervention was pen-and-paper exercises and oral cognitive tasks, though there were seven studies that used computerized exercises [24, 30, 31, 37-39, 53]. Additionally, one study used teleconference technology [40] and in four studies a family caregiver was the intervening agent [32, 41, 43, 44]. In few studies, participants continued training at home with the assistance of a family member [25, 28, 33]. In nine studies, the cognitive intervention was implemented solely in groups [27, 34, 36, 40, 42, 45, 48, 52, 53]. Participants were usually trained on multiple cognitive domains, most often memory, attention, executive functions, and language abilities. In six studies training was focused only on memory [26, 27, 28, 32, 35, 51], in two studies on semantic verbal processing [34, 40], and in one study on executive functions through reading aloud and solving arithmetic problems [46].

The 31 RCTs included 2132 participants in total, with the number of the participants varying from 11 [31] to 653 [52]. All studies included participants with clinically diagnosed or probable AD. In six studies, the diagnosis of the participants was AD or other, usually

vascular or Parkinson's dementia [23, 32, 33, 39, 42, 44], and in four studies participants were either AD or MCI patients [37, 39, 41, 45] (Table 2). Results are reported for the combined groups, as participants with different etiologies were inseparable in these trials. The mean age of the participants at baseline ranged from 67 to 86 years, with only one study reporting a mean age below 70 [24]. In most of the trials (n=22), the Mini-Mental State Examination (MMSE) mean score at baseline varied from 20 to 25, though three studies reported a mean score of 17-18 points [38, 47, 48]. Additionally, one study reported a mean score of 10 [39], one study a minimum of 10 [42] and two studies a range of 15-20 [27] and 2-29 [45]. The two remaining studies measured cognitive status with the Mattis Dementia Rating Scale (MDRS), with a minimum inclusion score of 90 [43] and 101 [44].

Methodological quality

As shown in Table 1, the 31 studies were rated as being of varying methodological quality overall. High quality studies were scarce in this review - only five trials were considered to be of high methodological quality, and nine trials were of moderate quality. Only one of the 19 studies utilizing restorative CT turned out to be of high quality, five were rated as being of moderate quality and the remaining 13 studies were of low quality. Studies, where CT was part of a multi-component intervention, were all rated as being of at least moderate quality, with three of the five being of high quality. Additionally, only one of the seven studies with the primary goal of compensating for cognitive impairments was of high methodological quality, and two were rated as being of moderate quality.

The most common methodological problems were very small sample sizes and poorly described randomization methods. Additionally, baseline characteristics of the randomized

groups and those who dropped out of the trials were often insufficiently described. Many studies gave only mean age and gender of the study participants at baseline. Further reasons for a poor quality rating were that dropouts were rarely included in the analyses, and that the intention-to-treat (ITT) analyses were infrequently used. Lastly, many studies utilized multiple tests to evaluate the outcome of their interventions, thus increasing the risk of false positive findings. However, most studies did sufficiently describe their intervention, the assessors evaluating the outcomes were usually blinded to the treatment allocation, and the outcome measures used were typically valid.

Effects of cognitive training

In total, 21 of the 31 studies reported a positive effect on at least one measure of cognitive outcome (Table 3). Additionally, 26 studies investigated the effects of CT on non-cognitive outcomes. Eight of the 26 studies reported a positive effect on affective status [33, 37, 38, 45, 47-49, 51], two on ADL [36, 46] or QoL [48, 50], and one on behavioral symptoms [49].

Cognitive training as the primary intervention: Of the 31 RCTs studied, 19 investigated the effects of restorative CT on cognition as the primary intervention. Two thirds of the 19 trials (n=13) reported at least one significant cognitive change relative to the control group (Table 3). None of the studies reporting significant improvement was of high methodological quality, however, and only five of these studies were rated as being of moderate methodological quality [28, 34, 36, 37, 47]. Additionally, six trials reported a non-cognitive positive outcome, typically on mood [37, 38, 47, 51] or ADL [36, 46].

Multi-component cognitive interventions: The five multi-component studies combining CT with other forms of intervention were generally of better quality than those focusing on restorative CT as the primary intervention. Additionally, the number and frequency of the intervention sessions was high in the multi-component trials. CT was combined with psychomotor activities [45], ADL training [29, 49], physical activity [48], reminiscence therapy [53] and other non-specific cognitive stimulation methods [29, 45, 47, 49, 53]. Of the five studies, four reported a positive effect on global cognition [29, 45, 49, 53], with one study also reporting an effect on working memory [29] and another study on episodic memory [53] (Table 3). Only one study reported no effect on cognition [48]. This study had a sample size of 14 participants with a low MMSE mean score of 18 at baseline assessment. Three of the five studies reported a positive effect on mood [45, 48, 49], one also on QoL [48], and one on behavioral symptoms [49].

Compensatory cognitive training: Studies with the primary goal of compensating for cognitive impairments typically reported a positive effect on training-specific tasks [32, 33, 41, 50], and not on standard cognitive outcome measures (Table 3). Of the seven predominantly low-frequency (i.e. one session a week) interventions in this category, only one found a positive association between training and global cognition using the MMSE Orientation subscale [50]. Additionally, in one trial, there was a positive association between training and mood [33], and in another study between training and QoL [50].

Five of the six studies with no effect on standard cognitive outcomes used short interventions (only 5-12 sessions in total) with a single training session a week [26, 27, 32, 33, 35]. In a more intensive in-home intervention with 24 sessions, the training focused on tasks relevant to real-world behaviors, having family caregivers participate in the training sessions and

reinforce learning between sessions [41]. A positive result, however, was only reported in training-specific outcome measures (e.g. recall of face-name associations, and balancing a checkbook with a calculator). In another intervention with spousal caregiver participation, the collaborative intervention group showed minor improvement in few training-related memory tasks, while the individual intervention group showed no effect [32].

Duration of the intervention: The duration of the cognitive intervention varied from 4 weeks [31] to 24 months [52] and the number of delivered sessions from 5 [26] to 103 [45] sessions. In total, 19 of the 31 studies used intervention programs with a minimum of 24 sessions (including guided in-home exercises). Of these, 14 studies reported a positive effect on cognition [28-30, 34, 36, 37, 40, 41, 43-46, 49, 53] and six on a functional outcome [36, 37, 45, 46, 48, 49], while five reported no effect [24, 25, 39, 48, 52]. In the trials reporting no effect, the baseline cognitive status was lower with a MMSE mean score ranging from 10 to 22.

Of the 12 studies with intervention programs less than 24 sessions long, seven trials found a positive effect on global cognition [31, 42, 47] or training-specific tasks [32, 33, 50, 51], while five studies found no cognitive benefit [23, 26, 27, 35, 38]. A non-cognitive benefit was reported in five studies, typically for mood [33, 38, 47, 51].

Frequency of the intervention: In 21 trials, the session frequency was twice a week or more. In one trial, there was a training session once a week plus additional systematic home exercises, resulting in multiple training sessions per week [25]. Altogether, 16 of the 22 studies with a high-frequency program reported a positive effect on at least one measure of cognitive outcome [28, 30, 31, 34, 36, 37, 40-47, 49, 53], while six trials failed to find any

significant effect on cognition [23-25, 38, 39, 48]. In these six trials the baseline cognitive status was quite low with a MMSE mean score ranging from 10 to 22. High-frequency programs predominated the trials, where a positive non-cognitive outcome was reported, with eight of the 11 effective programs using session frequency of twice a week or more [36-38, 45-49].

The remaining nine studies used low-frequency intervention programs, with only one session a week [26, 27, 29, 32, 33, 35, 50-52]. In one study stability of global cognition and working memory was reported, compared to a declining control group [29]. Two studies found a significant improvement in training-specific memory performance outcomes [32, 51]. In addition, two studies reported a positive training-specific outcome, which was measured by subjective ratings of goal performance and satisfaction with respect to ADL [33, 50] or by the MMSE orientation subscale [50].

Control condition: In more than half of the trials (n=18), the control group was offered activities, such as unstructured cognitive stimulation, at the same, or lower frequency as the intervention group, and the rest of the trials provided control groups with routine treatment only (Table 2). There were no clear associations between the activeness of the control group and the positive effects of the CT. However, four of the five multi-component trials compared their intervention with a passive control group; three of these showed a positive result [29, 49, 53].

Follow-up: All 31 studies measured cognitive outcomes immediately after the intervention period, and only 11 studies examined the maintenance of intervention gains [27, 28, 31, 33-35, 37, 38, 43, 51, 53]. The follow-up period after completion of the intervention was

relatively brief, varying from two weeks [51] to 9 months [31, 37] (Table 2). Cognitive functioning did show some sustainability at follow-up [28, 31, 34, 37, 51]; however, there was considerable variation with regard to duration of the interventions and length of follow-up periods in these few studies.

Domain-specific cognitive efficacy

A wide range of cognitive tests were used to evaluate cognitive change, with measures of global cognition, episodic memory and executive functions being the most frequent ones. A summary of the effects on various cognitive domains and training-specific tasks can be found in Table 3.

General cognitive functioning: MMSE was the most frequently used measure for the baseline cognitive status of the participants, as it was used in 29 of the 31 studies. When the baseline MMSE mean score was more than 22, a positive result in at least one cognitive outcome measure was reported in 10 of the 13 trials [28, 31, 33, 34, 37, 40, 41, 50, 51, 53]. Of the 14 trials with participants having a MMSE mean score of 22 or less, seven studies reported a positive result [29, 30, 32, 36, 46, 47, 49].

In total, 23 studies examined the effect of CT on global cognition, with 20 using the MMSE as a cognitive outcome measure as well. Significant change was reported in 13 of these 20 studies [28-31, 34, 36, 37, 40, 42, 45-47, 53]. Five studies used the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) [29, 30, 45, 49, 52], two studies the MDRS [41, 42], two the Milan Overall Dementia Assessment (MODA) [31, 36] and one study the Addenbrooke's Cognitive Examination-Revised (ACE-R) [39] as an outcome

measure for global cognition. A positive effect was observed in six of these 10 studies, four of those with the ADAS-Cog [29, 30, 45, 49], one with the MDRS [43] and one with the MODA [36].

In the moderate or high quality trials with CT as the primary intervention the ES of general cognitive functioning was large in three trials [32, 34, 45], and small in one trial [35]. In two studies, it was not possible to estimate the ES [26, 50]. In trials with cognitive training as part of a multi-component intervention, the ES was moderate in one trial [27], and small in three trials [46, 47, 51]. In one study it was not possible to calculate the ES [43]. One high quality study with the primary goal of compensating for cognitive impairments reported a small ES [33], whereas in one moderate quality study the ES could not be estimated [39], and another study did not have a global cognitive outcome in their study [31].

Memory: In total, 25 of the 31 intervention studies evaluated the effect of CT on learning and episodic memory (Table 3). In 23 studies, standard neuropsychological tests (clinically validated assessment tools, e.g. list learning or story recall) were used. Only five of the 23 studies reported a significant improvement on a measure of episodic memory [34, 40, 43, 44, 53]. In these five studies, the frequency of the intervention was at least twice a week. Barban et al. [53] used a combined CT and reminiscence therapy treatment, while Jelcic et al. [34, 40] focused on lexical-semantic exercises. In Quayhagen et al. studies [43, 44], the intensive cognitive intervention was executed or accompanied by a family caregiver.

One restorative CT trial used non-standardized outcome measures for semantic and episodic autobiographical memory, SAM and EAM, respectively [51], and one compensatory trial non-standardized object and word recall tasks [32]. Another training-specific episodic

memory outcome measure was recall of face-name associations [28, 41]. Two low-frequency treatments, which focused on autobiographical memory stimulation [51] and collaboratively practiced memory supportive strategies [32], reported having a positive effect on memory performance using measures quite similar to those trained for in the intervention. Another two studies found a positive effect on recalling face-name associations, a task again similar to those used in training [28, 41]. In one study, the participants' performance improved significantly on trained tasks during the intervention, but no differences between the intervention and the control groups were observed at the post-intervention assessment on any of the untrained cognitive tasks [25].

Ten studies evaluated the impact of CT on working memory (Table 3). As an outcome measure, nine studies used a digit span test and/or a visuospatial span test, while one study used the Brown-Peterson paradigm [36]. Only four of the 10 studies found a significant improvement in working memory [29, 34, 36, 40].

Executive functions: In total, 20 trials investigated the impact of CT on executive functions (Table 3). As an outcome measure, most studies used a verbal fluency task [25, 27, 30, 31, 33, 35-37, 39, 41, 42, 53], a few used the Trail-Making Test [27-29, 35, 40, 53] or the Stroop test [37], or both [34], and two studies used the Frontal Assessment Battery (FAB) [46, 48]. Additionally, measures for conceptualization [43, 44], reasoning [36] and decision-making [37] were used to evaluate the effects of CT on executive function and abstract thinking.

Only three studies found a positive effect of CT on executive functions. Two studies reported significant improvement in verbal fluency and reasoning [36], and decision-making [37]. The third study with a high-frequency intervention but quite small sample sizes, found modest

improvement in executive functioning after 6-months of intensive training on reading and arithmetic [46].

Attention: Attention tasks were used as outcomes in 13 studies (Table 3), but only one study found a significant improvement in processing speed relative to the control group [28]. The Continuous Performance Test (CPT), however, was also one of the training tasks in this intervention [29].

Language: Ten studies measured verbal skills as an outcome (Table 3), four of which found statistically significant group differences [34, 40, 43, 44]. A specific lexical-semantic treatment for 3 months with 2 sessions each week improved participants' global cognitive status, working memory, episodic memory and also verbal functions [34, 40].

Visual perception: Seven studies used tests of visual or visuospatial perception as an outcome (Table 3), yet only one reported a positive result. The experimental group scored significantly higher in several neuropsychological tests, including the Overlapping Figure Test and the Clock Drawing Test, after 12 months of repeated cycles of CT [36].

DISCUSSION

We reviewed 31 RCTs of CT for persons with AD or other dementias (usually vascular dementia). Most studies were conducted on patients with mild dementia. The 31 trials were highly heterogeneous in terms of content, duration, frequency and delivery of intervention, as well as in outcome measures and severity of baseline cognitive decline, making direct

comparisons difficult. Due to the variability of the interventions, it was not possible to perform a meta-analysis on this data.

In general, CT alone or when combined with other intervention methods may improve some aspects of cognition in AD patients. In total, 21 of the 31 trials reported a positive effect on at least one cognitive outcome, although multiple outcomes increased the risk of false positive findings in many effective trials. As noted before with healthy elderly persons, efficacy of CT varies across cognitive domains and is largely determined by intervention design choices [11]. In our review, more intense CT seemed to associate with more frequent cognitive benefits. For example, daily CT for 2-6 months at home [43, 44] or in a learning centre [46] resulted in positive effects on global cognition, episodic memory, and executive or language functions. In a more recent trial, intensive 1-month cycles of CT resulted in higher scores on global cognition and tests of working memory, executive and visuospatial functions, compared to the active control group [36]. Multiple cognitive outcomes were used in this study, with, however, six out of seven outcomes showing a positive effect after the intervention. With interventions less than 24 sessions, a significant change in cognition was rarely reported, and when identified, it was a minor change in global cognitive status or in a training-specific task.

Session frequency followed the same logic. In most trials the frequency was twice a week or more, resulting in a positive effect, most commonly, on global cognition and cognitive measures similar to exercises used in the intervention. When the CT frequency was once a week, the only reported benefits were training-specific [32, 33, 50, 51]. In a high-quality multi-centre trial in France, 653 patients were randomized to receive CT, reminiscence therapy, cognitive rehabilitation or treatment as usual [52]. The CT program, with one session

a week for the first 12 weeks and then one session every 6 weeks for the next 21 months, failed to show any cognitive benefit over standard care [52].

Multi-component trials typically used high-frequency interventions, and four of the five studies indicated a positive effect [29, 45, 49, 53]. For example, an intensive cognitive-motor program consisted of a 1-year structured program of 103 sessions of cognitive exercises together with a social and motor intervention [45]. Unfortunately, it was not possible to evaluate CT as a separate intervention in these multi-component trials. Moreover, an inactive control group increased the risk for a positive bias in three effective trials [29, 49, 53].

Studies with the primary goal of compensating for memory and other cognitive impairments seemed to have no effect on cognitive function per se, except having a positive effect on some training-specific tasks [32, 33, 41, 50]. This would be expected, since the main focus in these interventions was on improving performance in everyday life, and not to increase general cognition. However, only few positive functional outcomes were reported [33, 50]. Likewise, in a recent multi-centre trial, an individualized cognitive rehabilitation program provided a positive effect on functional, but not cognitive outcomes, while a structured CT program failed to show any effect [52].

A positive result was most often observed in global cognition, and was rarely observed in separate cognitive domains. The common improvement in global cognition was expected, since global cognitive measures (e.g. MMSE) briefly assess several cognitive functions, thus, detecting and summarizing changes in different cognitive domains. The magnitude of effect on global cognition varied considerably between the studies. Additionally, many trials reported improvement only on tasks in the same cognitive domain as training, some even on

similar tasks being trained, which is in accordance with the current understanding of the brain training effects [54]. These results would fit under near transfer effects of training. Far transfer effects to other than trained cognitive domains were reported in three trials. These specifically focused CT programs resulted in broader benefit for memory [34, 40] and executive functions [46]. Moreover, one third of the trials reported far effects to non-cognitive outcomes, typically to mood [33, 37, 38, 45, 47, 48, 49, 51], and in few cases to QoL [48, 50] and ADL [36, 46].

The common problem of low methodological quality of the trials reviewed limits the evaluation of the evidence, resulting in inadequate statistical power and an increased risk of false positive findings. More than half of the studies were rated as being of low quality, while only five studies were considered to be of high quality (see Table 1). Definitions and degrees of dementia varied resulting in heterogeneous groups of participants. Additionally, the typical lack of follow-up may also provide overly optimistic conclusions regarding the effectiveness and clinical relevance of the CT interventions. However, the more recent CT trials did show a trend towards larger samples and higher methodological quality.

The present study has some limitations. A rigorous search strategy and broad inclusion criteria for this review resulted in 31 RCTs. We relied on published reports only, which may positively skew our results toward a publication bias. A language bias through selecting only papers reported in English is evident. Classification of the cognitive interventions was based on the definitions suggested by Clare and Woods [7], though a wide range of ambiguity still remained in classifying the included CT programs. Another potential limitation is the variability in the range of disease severity across studies. All the trials included AD patients, but there were also a few trials using participants with mixed dementia diagnosis.

Additionally, the considerable variation in duration of the treatments and length of follow-up, if any, limits the evaluation of the long-term effects of the interventions. Consequently, it is unclear whether reported positive effects are sustainable over time.

Conclusions

The intention of using CT in neurodegenerative disorders is to delay deterioration of cognition and support independent living. We reviewed RCTs of restorative and compensatory CT in AD and other dementias, and found the prevailing heterogeneity and diversity of the training programs in combining different intervention methods and strategies. As Kurz et al. [12] concluded, the inconsistency of CT trials regarding sample sizes, duration of interventions, number of treatment sessions, intervention focuses and contents, control conditions, settings, outcome measures and cognitive domains assessed does not allow firm conclusions regarding the effects of CT. In future studies, both exact definition and harmonization of CT programs is needed for enabling more definite conclusions and true comparability across interventions.

The current body of evidence suggests that CT may lead to observable improvements in the global cognitive status of individuals with AD, as well as enhanced performance in tasks similar to the trained exercises. These effects seem to result from longer and more intensive training programs. It also seems, that shorter interventions focusing on a specific aspect of cognitive functions may lead to specifically targeted effects. The generalization of the treatment effects beyond the trained cognitive tasks remains to be demonstrated. Moreover, future large-scale RCTs with long-term follow-up are required to confirm whether CT can

improve cognitive functioning, delay further disease progression and help individuals to manage their daily routines.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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Table 1

Quality criteria fulfillment of the trials examining the effects of cognitive training on Alzheimer's patients.

Study	Criteria†										Total
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	
Studies with cognitive training as the primary intervention											
Beck et al. [23]	+/-	+/-	-	-	-	+/-	-	+	+	-	2
Breuil et al. [42]	+	+/-	+	-	+	+/-	+	+/-	+/-	+/-	4
Heiss et al. [24]	+	+/-	-	-	-	+	-	-	-	+/-	2
Quayhagen et al. [43]	+	+/-	+/-	-	+	+/-	+	-	-	+	4
Quayhagen et al. [44]	+/-	+/-	-	-	+	+/-	+	+/-	+/-	+	3
Davis et al. [25]	+/-	+/-	-	-	+	+	+	+/-	+/-	+	4
Loewenstein et al. [28]	+	+/-	-	-	+	+	+	+/-	+/-	+	5
Kawashima et al. [46]	+/-	+	-	-	+	+/-	-	+/-	+/-	-	2
Tárraga et al. [30]	+	+/-	-	-	+	+	+	-	-	-	4
Galante et al. [31]	+/-	+/-	-	+	+	+	+	-	+/-	-	4
Niu et al. [47]	+	+	-	+	+	+/-	+	+	+	-	7
Jelcic et al. [34]	+	+	-	+	+	+	+	+/-	+	-	7
Bergamaschi et al. [36]	+	+	-	+	+	+	+	+/-	+/-	+	7
Gaitán et al. [37]	+	+/-	-	+	+	+	+	+/-	+/-	+	6
Lee et al. [38]	+	+/-	-	-	+	+	+	+/-	+/-	-	4
Zhuang et al. [39]	+/-	+	-	-	+	+/-	+	+/-	-	-	3
Jelcic et al. [40]	+	+/-	-	-	+	+	+	+/-	+/-	-	4
Lalanne et al. [51]	+/-	+	-	-	+	+/-	-	-	+/-	+	3

Study	Criteria†										Total
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	
Amieva et al. [52]	+	+	+	+	+	+	+	+/-	+	+	9
Studies with cognitive training as part of a multi-component intervention											
Olazarán et al. [45]	+	+	+	+	+	+	+	+	+	+	10
Bottino et al. [29]	+	+/-	-	+	+	+	+	+/-	+/-	+/-	5
Maci et al. [48]	+	+/-	-	+/-	+	+	+	+/-	+/-	+	5
Fernández-Calvo et al. [49]	+	+	+	+	+	+	+	+	+/-	+	9
Barban et al. [53]	+	+	+	+	+	+	+	-	-	+	8
Studies with the primary goal of compensating for cognitive impairments											
Koltai et al. [26]	+	+/-	-	-	+	+	+/-	-	+/-	-	3
Cahn-Weiner et al. [27]	+/-	+/-	-	+/-	+	+	+	-	-	+/-	3
Neely et al. [32]	+	-	-	+/-	+	+/-	-	+/-	+/-	+/-	2
Clare et al. [33]	+	+	-	+	+	+	+	+	+/-	+/-	7
Kurz et al. [35]	+	+/-	+	+	+	+	+	+	+/-	+	8
Tappen and Hain [41]	+/-	+	+	-	+	+	+	+/-	-	+	6
Kim [50]	+/-	+	-	-	+	+	+	+/-	+/-	-	4

† Criteria: (1) The inclusion and exclusion criteria are satisfactorily described and the diagnosis of dementia is based on DSM-IV (American Psychiatric Association, 1994) or NINCDS-ADRDA [22] criteria. (2) Groups are comparable at baseline. (3) The study has sufficient statistical power to detect an effect (n > 25/group) or an adequate power calculation is presented. (4) The randomization method is valid and adequately described. (5) The intervention is adequately described. (6) The measurements and outcome measures are valid and well defined. (7) Those assessing the outcomes are blind to the treatment allocation. (8) Outcomes of the dropouts are described and the analysis takes them into

account. (9) An intention-to-treat (ITT) analysis is applied. (10) Appropriate statistical analyses are used.

+, Criterion fulfilled; +/-, criterion partly fulfilled; -, criterion not fulfilled.

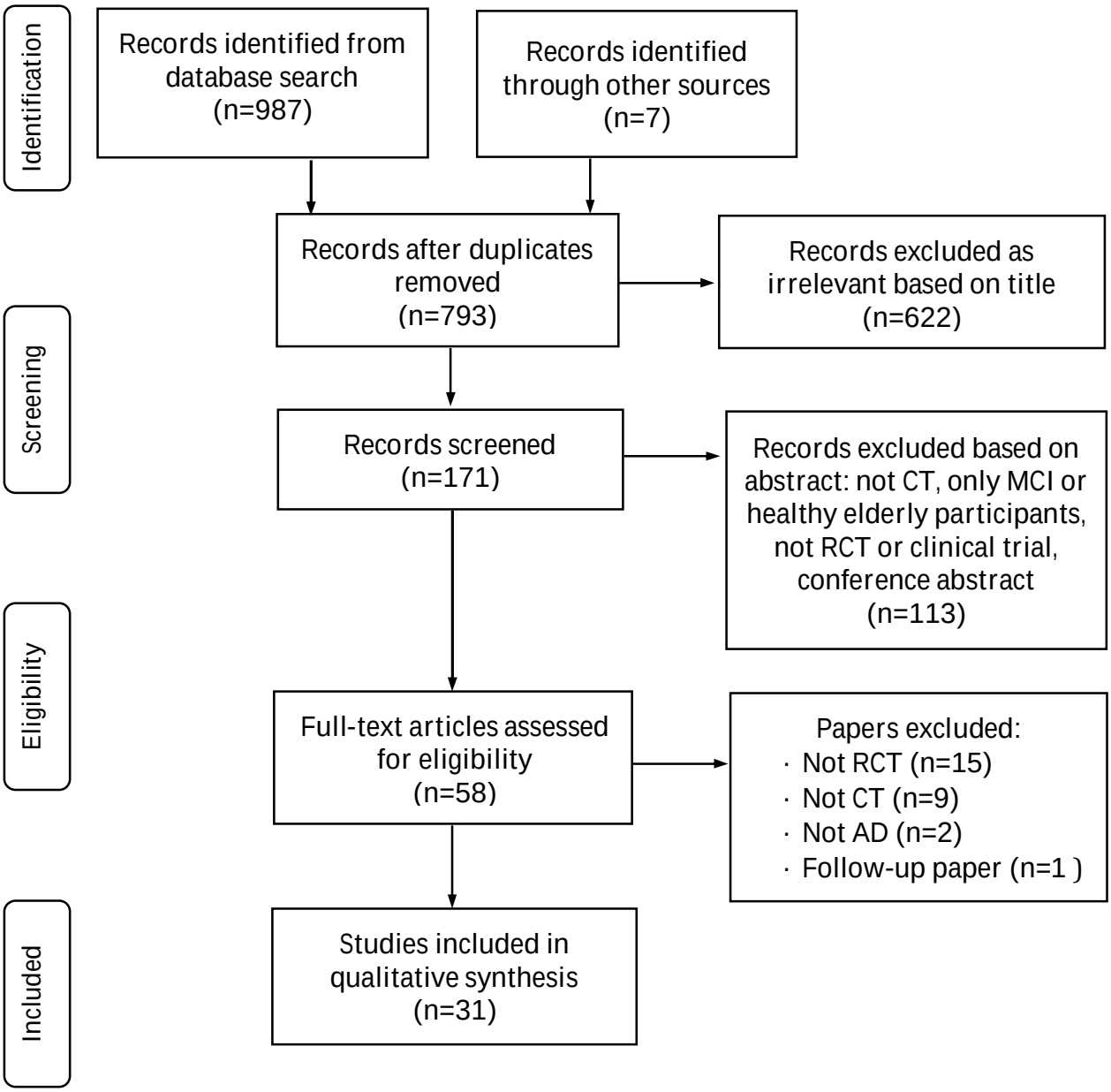

Fig. 1. The flow chart of our systematic review. A single study could be excluded on more than one criterion, but appears only once in the chart.

Table 2

Study characteristics and main outcomes.

Study	**Participants**[†]	**Diagnosis**[††]	**Intervention**	**Control group(s)**	**Assessment time**[†††]	**Main outcomes**	**Quality rating**[††††]
Studies with cognitive training as the primary intervention							
Beck et al. 1988 [23]	*n*=20 F 60 % 75 years MMSE 15-20	AD or mixed dementia	Cognitive skills remediation training in attention, reading, concentrating on detail and remembering (*n*=10). *CT: 6 weeks, 3 times a week, 18 sessions, 30-40 min, individual.*	Passive. Treatment as usual (*n*=10).	Post-interv.	No significant association between CT and cognitive outcome. Trend towards improvement in one measure of memory (digit span).	Low
Breuil et al. 1994 [42]	*n*=61 F 61 % 77 years MMS > 9	AD (92 %), multi-infarct, Parkinson, mixed or other dementia	Global cerebral stimulation using mental imagery in its visual and semantic modes to stimulate encoding, consolidation and retrieval of information (*n*=32). *CT: 5 weeks, twice a week, 10 sessions, 60 min, in groups.*	Passive. Non-stimulated control (*n*=29).	Post-interv.	Significant improvement in global cognition (MMS). No effect on word list memory or verbal fluency. Discarded 5 items of CERAD battery because of a ceiling or floor effect.	Low

Heiss et al. 1994 [24]	*n*=70 F 47 % 67 years MMSE 21	AD	Computerized cognitive training covering memory, perceptual and motor tasks (*n*=18). Additional interventions: CT plus pharmacological treatment of pyritinol (*n*=17) or phosphatidylserine (*n*=18). *CT: 24 weeks, twice a week, 48 sessions, 60 min, individual.*	Active. Social support 1h once a week (*n*=17).	8 wk 16 wk Post-interv.	No significant change in any neuropsychological test in the CT group. The group that received CT combined with pharmacological treatment showed some cognitive effect. Multiple tests used.	Low
Quayhagen et al. 1995 [43]	*n*=78 F 35 % 74 years MDRS ≥ 90	AD	In-home dyadic cognitive stimulation program of memory, problem solving and conversation activities executed by a family caregiver (*n*=25). Additional 12 sessions (once a week) for the family to train program implementation techniques. *CT: 12 weeks, 6 times a week, 72 sessions, 60 min, individual.*	Active. Cognitive stimulation (*n*=28). Passive. Waiting-list control (*n*=25).	Post-interv. 6 mo f/u	Improvement in global cognitive function (MDRS) and composite scores of general and non-verbal memory and verbal fluency at post-intervention. Return to baseline at 9 months. Active control group maintained baseline status on some items while others declined. Waiting-list group declined on all measures. Multiple tests used.	Low

Quayhagen et al. 2000 [44]	*n*=103 F 63 % 75 years MDRS > 100	AD (70 %), multi-infarct or Parkinson dementia	Home-based cognitive stimulation program for the caregiver-patient dyad focusing on memory, problem solving and conversational fluency, with the caregiver as the intervening agent (*n*=21). *CT: 8 weeks, 5 times a week, 40 sessions, 60 min, individual*.	Active. Dyadic counseling (*n*=29), early day-care (*n*=16) or dual seminar (*n*=22). Passive. Waiting-list control (*n*=15).	Post-interv.	Persons in the cognitive stimulation program showed improvement in composite cognitive scores of delayed memory and verbal fluency at post-intervention compared with other study groups.	Low
Davis et al. 2001 [25]	*n*=37 F 57 % 71 years MMSE 22	AD	Cognitive training in personal information, face-name associations and mnemonic strategy combined with in-home attention exercises (*n*=19). *CT: 5 weeks, once a week, 5 sessions,*	Active. Unstructured conversation and psycho-education (*n*=18).	Post-interv.	No significant group differences at post-intervention on any of the untrained cognitive outcomes. Improvement seen as enhanced recall of personal information and face-name associations during the 5-week	Low

			60 min, individual plus additional home exercises 6 times a week, 30 min.			intervention.	
Loewenstein et al. 2004 [28]	*n*=44 F 41 % 77 years MMSE 24	AD	Cognitive rehabilitation focusing on face-name associations, orientation, use of a memory book, bill-paying, procedural memory and visuomotor processing (*n*=25). Additional in-home training with assistance of a family member was encouraged. *CT: 12-16 weeks, twice a week, 24 sessions, 45 min, individual.*	Active. Mental stimulation with computer games and word-finding games (*n*=19).	Post-interv. 3 mo f/u	Improvement in orientation (MMSE), recall of face-name associations, change for purchase and processing speed (CPT) at post-intervention, which was maintained at 3-month follow-up. No group differences on any of the untrained cognitive tasks. Multiple tests used.	Moderate
Kawashima et al. 2005 [46]	*n*=32 F not reported 86 years MMSE 20	AD	Learning therapy using systematized basic problems in reading and arithmetic (*n*=16). *CT: 6 months, 2-6 times a week, 20 min, individual.*	Passive. Treatment as usual (*n*=16).	Post-interv.	Improvement reported in executive functions (FAB). Mean MMSE score remained stable for the intervention group but declined in the control group. Restoration of an independence score (NM scale) was also reported.	Low

Tárraga et al. 2006 [30]	*n*=46 F 85 % 77 years MMSE 22 ADAS-Cog 21	AD	Interactive multimedia internet-based system (IMIS) for cognitive training covering domains of attention, calculation, gnosis, language, memory and orientation (*n*=15). *CT: 24 weeks, 3 times a week, 72 sessions, 20 min, individual.*	Active. Integrated psychostimulation in groups (*n*=16). Passive. Standard care (*n*=12).	12 wk Post-interv.	The IMIS program provided improvement (ADAS-Cog, MMSE) after 12 weeks and stability at post-intervention (at week 24). The psychostimulation provided improvement at week 12, but the result attenuated at week 24. In the standard care group global cognition declined both at week 12 and 24. Multiple tests used.	Low
Galante et al. 2007 [31]	*n*=11 F not reported 76 years MMSE 23 MODA 82	AD	Computer-based cognitive intervention covering attention, perception, memory, language and spatial cognition (*n*=7). *CT: 4 weeks, 3 times a week, 12 sessions, 60 min, individual.*	Active. Semi-structured interviews on current topics and life events (*n*=4).	Post-interv. 3 mo f/u 9 mo f/u	Mean MMSE score remained stable in the intervention group at 9-month follow-up, but declined in the control group. No effects on other cognitive outcomes or at other time intervals. Multiple tests used.	Low
Niu et al.	*n*=32	AD	Cognitive stimulation therapy	Active.	Post-interv.	Patients receiving cognitive	Moderate

2010 [47]	F 22 % 80 years MMSE 17		focusing on tasks requiring executive functions and working memory: orientation, verbal fluency, overlapping figures and story learning (*n*=16). *CT: 10 weeks, twice a week, 20 sessions, 45 min, individual.*	Communication exercises on current topics, and psycho-education (*n*=16).		stimulation therapy showed improvement on global cognition (MMSE score). Also, NPI total score improved at post-intervention: a statistically significant benefit of the intervention was reported in the domains of apathy and depression.	
Jelcic et al. 2012 [34]	*n*=40 F 83 % 82 years MMSE 25, CDR 0.5 - 1	AD	Lexical-semantic stimulation (LSS) with a wide range of lexical tasks aimed at enhancing semantic verbal processing (*n*=20). *CT: 3 months, twice a week, 60 min, in groups.*	Active. Unstructured cognitive stimulation (*n*=20).	Post-interv. 6 mo f/u	Global cognition (MMSE), naming abilities (BNT, VNT) and verbal episodic memory (story recall) improved in LSS group at post-intervention. At 6-month follow-up MMSE score remained significantly higher than at baseline. Multiple tests used.	Moderate
Bergamaschi et al. 2013 [36]	*n*=32 F not reported 78 years MMSE 21	AD	Cognitive training in spatial orientation, memory, logical reasoning, attention, perception, visual analysis and recognition of	Active. Non-specific cognitive activity at a	Post-interv.	After repeated cycles of training the intervention group showed significant improvement on six out of seven cognitive outcomes (MMSE, MODA,	Moderate

			emotional expressions (*n*=16). *CT: Five 1-month cycles of 20 sessions, 5 times a week, 120 min, with a break of 4 weeks between each cycle, in groups.*	day centre (*n*=16).		short-term memory, verbal fluency, visual organization and clock drawing), and stability of ADL, compared to the control group.	
Gaitán et al. 2013 [37]	*n*=39 F 51 % 76 years MMSE 25	AD (31 %) or MCI	Computer-based cognitive training in attention, memory and executive functions combined with conventional pen-and-paper exercises (*n*=23). *CT: 12 weeks, 2-3 times a week, 30 sessions, 60 min, individual plus conventional CT exercises during 12 months, 2-3 times a week, 60 min, in groups.*	Active. Conventional pen-and-paper exercises (*n*=16).	Post-interv. 9 mo f/u	Computer-based intervention showed a positive effect at post-intervention on global cognition (less deterioration of MMSE score), decision making (less IGT Deck A choices) and anxiety symptoms (STAI-S). Other outcomes showed no effect. Multiple tests used.	Moderate
Lee et al. 2013 [38]	*n*=19 F 68 % 78 years MMSE 17,	AD	Errorless learning -based memory training program with a computer (*n*=6). Additional intervention group: therapist-led training program (*n*=6).	Passive. Waiting-list control (*n*=7).	Post-interv. 3 mo f/u	No significant association between CT program and cognitive outcome was found. Reported a positive effect on mood (GDS) at post-intervention.	Low

	CDR 1		*CT: 6 weeks, twice a week, 12 sessions, 30 min, individual.*				
Zhuang et al. 2013 [39]	*n*=33 F 76 % 83 years MMSE 10	AD or vascular dementia (39 %), or MCI	Human-computer interaction-based comprehensive cognitive training on picture memorization, sorting, sequencing, drawing and opening a virtual door (*n*=19). *CT: 24 weeks, 3 times a week, 72 sessions, 75 min, individual.*	Treatment not reported (*n*=14).	Post-interv.	No significant association between CT and cognitive outcome.	Low
Jelcic et al. 2014 [40]	*n*=27 F 78 % 83 years MMSE 24, CDR 0.5 - 1	AD	Lexical-semantic stimulation (LSS) enhancing verbal semantic processing through a teleconference technology (*n*=7). Additional intervention group: face-to-face LSS intervention (*n*=10). *CT: 3 months, twice a week, 60 min, in groups.*	Active. Unstructured cognitive stimulation (*n*=10).	Post-interv.	Positive effects (improvement) at post-intervention were reported on global cognition (MMSE), language abilities (VNT), immediate story recall, delayed RAVL recall and working memory. Multiple tests used.	Low
Lalanne et al. 2015 [51]	*n*=33 F not reported 72 years	AD	Cognitive training program for autobiographical memory (REMau) on both episodic and semantic	Active. Cognitive training	Post-interv. 2 wk f/u	REMau program improved autobiographical memory performance on two different tasks	Low

	MMSE 25		aspects of autobiographical memory across all life periods (*n*=16). *CT: 6 weeks, once a week, 6 sessions, 60 min, individual.*	focusing on collective semantic memory (*n*=17).		(SAM, EAM), as well as mood (GDS). Improvement was maintained at 2 weeks follow-up.	
Amieva et al. 2016 [52]	*n*=653 F 60 % 79 years MMSE 22	AD	Cognitive training therapy designed to involve various cognitive functions (memory, attention, language, or executive function) (*n*=170). Additional interventions: individualized cognitive rehabilitation therapy (*n*=157) or reminiscence therapy in groups (*n*=172). *CT: 24 months in total, for 3 months 1 session a week, then for 21 months 1 session every 6 weeks, 90 min, in groups.*	Passive. Treatment as usual (*n*=154).	3 mo Post-interv.	No impact on the cognitive outcome (ADAS-Cog) was evidenced in CT (or any other) group. Cognitive rehabilitation group showed slower functional decline and reduced rates of institutionalization at post-intervention compared to other groups.	High
Studies with cognitive training as part of a multi-component intervention							

Olazarán et al. 2004 [45]	*n*=84 F 60 % 74 years MMSE 2 – 29 ADAS-Cog 25	AD (86 %) or MCI	Cognitive-motor intervention (CMI) including cognitive exercises (on e.g. memory, attention, and executive functions) combined with 3 hours of ADL-training, social and psychomotor activities (*n*=44). *CT: 12 months, twice a week, 103 sessions, 30 min, in groups.*	Active. Psychosocial support (*n*=40).	1 mo 3 mo 6 mo Post-interv.	Patients in the CMI group maintained cognitive status (MMSE, ADAS-Cog) during the intervention at month 6, whereas the control group declined. At post-intervention, the only positive effect of CMI was on affective status (GDS, NPI).	High
Bottino et al. 2005 [29]	*n*=13 F 69 % 74 years MMSE 22, ADAS-cog 21 CDR 0.5 - 1	AD	Cognitive rehabilitation focusing on orientation, face-name associations, memory strategies and use of external memory aids combined with ADL training and cognitive stimulation (*n*=6). *CT: 5 months, once a week, 90 min, in groups.*	Passive. Routine treatment (*n*=7).	Post-interv.	Intervention group showed a positive treatment effect (no deterioration) on two cognitive measures (MMSE, digit span backwards). Multiple tests used.	Moderate
Maci et al. 2015 [48]	*n*=14 F 57 % 73 years	AD	Training of spatiotemporal orientation, memory, executive skills and language combined with 2 hours	Passive. Routine medical	Post-interv.	No significant association between CT and cognitive outcome was found. Apathy (AES), anxiety	Moderate

	MMSE 18		of physical activity and group discussions (*n*=7). *CT: 3 months, 5 times a week, 60 min, in groups.*	practice (*n*=7).		(HAM-A) and depression (CSDD) decreased, and QoL (QoL-AD) increased after the treatment.	
Fernández-Calvo et al. 2015 [49]	*n*=61 F 57 % 73 years MMSE 22, CDR 1	AD	Multi-component home-based intervention program using cognitive exercises, restorative and compensatory memory strategies combined with 50 minutes of social, functional and recreational activities (*n*=28). *CT: 16 weeks, 3 times a week, 48 sessions, 40 min, individual.*	Passive. Waiting-list control (*n*=33).	Post-interv.	The intervention group displayed significantly less cognitive decline (ADAS-cog), and a reduction in behavioural (NPI-Q) and depressive (CSDD) symptoms at post-intervention.	High
Barban et al. 2016 [53]	*n*=81 F 70 % 77 years MMSE 23, CDR 1	AD	Computerized process-based cognitive training (pb-CT) for memory, executive and other cognitive functions combined with reminiscence therapy (n=42). *CT: 3 months, twice a week, 24*	Passive. Waiting-list control (*n*=39).	Post-interv. 3 mo f/u	Positive effect at post-training for two cognitive outcomes: episodic verbal memory (RAVLT) and global cognition (MMSE). Improvements not maintained at 3-month follow-up.	High

			sessions, 30 min (pb-CT), in groups.				
Studies with the primary goal of compensating for cognitive impairments							
Koltai et al. 2001 [26]	*n*=24 F not reported 73 years MMSE 24, CDR 0.5 - 1	AD	Memory and coping program addressing cognitive and affective functioning individually (*n*= 8) or in groups (*n*= 8). *CT: 5 weeks, once a week, 5-6 sessions, 60 min, individual or in groups.*	Passive. Waiting-list control (*n*= 8).	Post-interv.	No significant association between CT, and cognitive or other outcome.	Low
Cahn-Weiner et al. 2003 [27]	*n*=34 F 58 % 77 years MMSE 25	AD	Memory training program using visualization and categorization techniques (*n*=17). *CT: 6 weeks, once a week, 6 sessions, 45 min, in groups.*	Active. Psychoeducation in groups with no memory training (*n*=17).	Post-interv. 8 wk f/u	No significant effect on any of the neuropsychological outcome measures at post-intervention or follow-up. Some gains in memory performance during the 6-week memory training. Multiple tests used.	Low
Neely et al. 2009 [32]	*n*=30 F 50 % 75 years	AD or vascular dementia	In-home individual intervention program focusing on learning strategies in a face-name task and a	Passive. No intervention (*n*=10).	Post-interv.	After the individual intervention, no improvements occurred as a function of training. Participants in the	Low

	MMSE 21		table setting activity (*n*=10). Additional intervention: Collaborative intervention program involving the caregiver with the same training regimen as in the individual program (*n*=10). *CT: 8 weeks, once a week, 8 sessions, 60 min, individual.*			collaborative intervention did show improvement in one of the four training-related memory tasks (recall of categorizable words).	
Clare et al. 2010 [33]	*n*=69 F 59 % 78 years MMSE 23	AD (80 %), or mixed AD/vascular dementia	Goal-oriented cognitive rehabilitation conducted in participants' homes (*n*=23). CT focused on new learning and attention. Participants were encouraged to work on goals and practice strategies between sessions. *CT: 8 weeks, once a week, 8 sessions, 60 min, individual.*	Active. Relaxation therapy (*n*=24). Passive. No treatment (*n*=22).	Post-interv. 6 mo f/u	Improvement in subjective ratings of goal performance and satisfaction (COPM), as well as decreased anxiety (HADS), compared to two control groups at post-intervention. No positive effect on any of the cognitive outcomes.	Moderate
Kurz et al. 2012 [35]	*n*=201 F 44 %	AD	Intervention combined strategies of neurorehabilitation and	Passive. Standard	Post-interv. 6 mo f/u	No effect of the intervention on the participants' cognitive ability or	High

	74 years MMSE 25		psychotherapy: use of external memory aids, establishing behavioral routines, activity planning and reminiscence therapy (*n*=100). *CT: 12 weeks, once a week, 12 sessions, 60 min, individual.*	medical management (*n*=101).		ability to perform ADL. Positive effect on depressive symptoms (GDS) only among female participants at post-intervention and at 6-month follow-up.	
Tappen and Hain 2014 [41]	*n*=68 F 40 % 81 years MMSE 25, CDR ≤ 1	AD or MCI	In-home cognitive training with caregivers using spaced retrieval paradigm, functional task training and compensatory memory strategies (*n*=37). Training focused on tasks directly relevant to real-world behaviors. *CT: 12 weeks, twice a week, 24 sessions, 60 min, individual.*	Active. Organized, sequential life story interviews (*n*=31).	Post-interv.	Improvement in tasks specifically trained for (face-name recognition, making change, balancing a checkbook, prospective memory). No significant changes on other outcome measures. Multiple measures used.	Moderate
Kim 2015 [50]	*n*=43 F 65 % 71 years MMSE 23*	AD	Goal-oriented cognitive rehabilitation combined with practicing orientation, face-name associations, learning memory and sustained attention	Active. Unstructured conversation and health-	Post-interv.	Orientation (MMSE) improved in the cognitive rehabilitation group. Improvement also reported on subjective ratings of goal	Low

	(*n*=22). *CT: 8 weeks, once a week, 8 sessions, 30 min individual and 30 min in groups.*	related videos (*n*=21).	performance and satisfaction (COPM), and QoL (QoL-AD), compared to control group. No improvement on memory performance.

[†] Number (*n*), % female (F), mean age and baseline cognitive status of the participants. [††]The percentage of participants with AD is reported for the trials using combined patient groups (when available), [†††] Outcome assessment times in chronological order, [††††]Low = 0-4/10, Moderate = 5-7/10 and High = 8-10/10 points in our rating scale of methodological quality, wk = weeks, mo = months, Post-interv. = at post-intervention, f/u = follow-up.

AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale - Cognitive subscale; ADL, activities of daily living; AES, Apathy Evaluation Scale; BNT, Boston Naming Test; CERAD, The Consortium to Establish a Registry for Alzheimer's Disease; CDR, Clinical Dementia Rating; COPM, Canadian Occupational Performance Measure; CPT, Continuous Performance Test; CSDD, Cornell Scale for Depression in Dementia; CT, cognitive training; EAM, Episodic autobiographical memory; F, female; FAB, Frontal Assessment Battery; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Anxiety rating scale; IGT, Iowa Gambling Task; MCI, mild cognitive impairment; MDRS, Mattis Dementia Rating Scale; MMS or MMSE, Mini Mental State Examination; MODA, Milan Overall Dementia Assessment; NM scale, Nishimura Mental State Scale for the Elderly; NPI, Neuropsychiatric Inventory; NPI-Q, Neuropsychiatric Inventory Questionnaire; QoL, quality of life; QoL-AD, Quality of Life-Alzheimer's Disease; RAVL(T), Rey Auditory Verbal Learning Test; SAM, Semantic autobiographical memory; STAI-S, State-Trait Anxiety Inventory State; VNT, Verbal Naming Test.

Table 3

Effects of cognitive interventions on different domains of cognition, and non-cognitive outcomes.

Study	Cognitive domains assessed with standard cognitive measures[1]								
	General cognitive functioning	Executive functions	Attention	Working memory	Episodic memory	Language	Visual perception	Training-specific measures[2]	Non-cognitive measures[3]
Studies with CT as the primary intervention									
Beck et al. [23]			0	0	0		0		
Breuil et al. [42]	+	0			0				0
Heiss et al. [24]	0		0	0	0	0			
Quayhagen et al. [43]	+	0			+	+			0
Quayhagen et al. [44]		0			+	+			0
Davis et al. [25]	0	0	0	0	0				0
Loewenstein et al. [28]	+	0	+	0	0			+[4]	0
Kawashima et al. [46]	+	+							+
Tárraga et al. [30]	+	0	0		0	0			0
Galante et al. [31]	+	0	0	0	0				0
Niu et al. [47]	+								+
Jelcic et al. [34]	+	0	0	+	+	+	0		0
Bergamaschi et al. [36]	+	+		+	0		+		+

Study	Cognitive domains assessed with standard cognitive measures[1]								
	General cognitive functioning	Executive functions	Attention	Working memory	Episodic memory	Language	Visual perception	Training-specific measures[2]	Non-cognitive measures[3]
Gaitán et al. [37]	+	+	0	0	0		0		+
Lee et al. [38]	0				0				+
Zhuang et al. [39]	0	0	0		0	0	0		
Jelcic et al. [40]	+	0	0	+	+	+	0		
Lalanne et al. [51]								+[5]	+
Amieva et al. [52]	0								0
Studies with CT as part of a multi-component intervention									
Olazarán et al. [45]	+								+
Bottino et al. [29]	+	0		+	0	0			0
Maci et al. [48]	0	0							+
Fernández-Calvo et al. [49]	+								+
Barban et al. [53]	+	0			+				0
Studies with a primary goal of compensating for cognitive impairments									
Koltai et al. [26]	0				0				0
Cahn-Weiner et al. [27]		0	0		0	0	0		0
Neely et al. [32]								+[6]	
Clare et al. [33]		0	0		0			+[7]	+
Kurz et al. [35]	0	0	0		0				0

Study	Cognitive domains assessed with standard cognitive measures[1]								
	General cognitive functioning	Executive functions	Attention	Working memory	Episodic memory	Language	Visual perception	Training-specific measures[2]	Non-cognitive measures[3]
Tappen and Hain [41]		0			0	0		+[8]	0
Kim [50]	+[9]				0			+[7]	+

+ = Significant effect for experimental group; 0 = No difference between intervention and control groups.

[1] Cognitive outcome measures used in detecting significant effects: ADAS-Cog, MDRS, MMSE, MODA (General cognitive functioning); FAB, IGT, verbal fluency, Clock Drawing Test (Executive functions); CPT (Attention); digit span, memory test with interference (Working memory); Brief story recall, CERAD list learning, RAVL(T), WMS-R (Episodic memory); BNT, VNT (Language); Overlapping Figure Test (Visual perception).

[2] Training-specific measures refer to tasks similar to exercises used in CT.

[3] Non-cognitive measures used in detecting significant effects: AES, CSDD, GDS, HADS, HAM-A, NPI, NPI-Q, STAI-S (Mood), ADL index, NM scale (ADL functions), QoL-AD (QoL).

[4] Recall of face-name associations, Orientation, Change-for-purchase test

[5] Measures of semantic (SAM) and episodic autobiographical memory (EAM)

[6] Recall of categorizable words

[7] COPM

[8] Recall and recognition of face-name associations, Making change, Balancing checkbook, Event-related prospective memory

[9] MMSE Orientation subscale

ADAS-Cog, Alzheimer’s Disease Assessment Scale - Cognitive subscale; ADL, activities of daily living; AES, Apathy Evaluation Scale; BNT, Boston Naming Test; CERAD, The Consortium to Establish a Registry for Alzheimer's Disease; COPM, Canadian Occupational Performance Measure; CPT, Continuous Performance Test; CSDD, Cornell Scale for Depression in Dementia; CT, cognitive training; EAM, Episodic autobiographical memory; FAB, Frontal Assessment Battery; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Anxiety rating scale; IGT, Iowa Gambling Task; MDRS, Mattis Dementia Rating Scale; MMSE, Mini Mental State Examination; MODA, Milan Overall Dementia Assessment; NM scale, Nishimura Mental State Scale for the Elderly; NPI, Neuropsychiatric Inventory; NPI-Q, Neuropsychiatric Inventory Questionnaire; QoL, quality of life; QoL-AD, Quality of Life-Alzheimer’s Disease; RAVL(T), Rey Auditory Verbal Learning Test; SAM, Semantic autobiographical memory; STAI-S, State-Trait Anxiety Inventory State; VNT, Verbal Naming Test; WMS-R, Wechsler Memory Scale-Revised.